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National Cancer Institute

Adult Kidney Cancer and Wilms' Tumor

Research Report

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Introduction

This *Research Report* describes current research on the causes and prevention, symptoms, diagnosis, and treatment of kidney cancers in adults and children. The information presented here was obtained from medical textbooks and recent articles in the medical literature, discussions with National Cancer Institute (NCI) scientists and other researchers, and various scientific meetings.

This *Report* provides more detailed information about cancers of the kidney than is contained in the patient-oriented pamphlets, *What You Need to Know About Cancer of the Kidney* and *What You Need to Know About Wilms' Tumor.*

This *Research Report* was written by Linda C. Slan under contract with the National Cancer Institute. The scientific content of this publication has been approved by NCI scientists. Please direct questions or comments to the *Research Reports* editor, National Cancer Institute, Office of Cancer Communications, Bethesda, MD 20892.

Description and Function of the Kidneys

The kidneys are a pair of purplish-brown organs located behind the abdominal cavity on each side of the spine, just above the waist. Enclosed by a capsule of fibrous connective tissue called Gerota's fascia, each kidney is cushioned by layers of fatty tissue. The kidney of a 3-year-old child is about 2 inches long, 1 inch wide, and weighs about 4 ounces. The adult kidney is 4 to 5 inches long, 2 to 3 inches wide, and weighs 6 to 8 ounces.

The firm outer region of the kidney, the cortex, makes up about a third of the kidney tissue. The inner portion, called the medulla, has a hollow center, known as the renal pelvis. An indentation in the side of each kidney, the renal hilum, is the passageway for nerves and the vessels that carry blood into and away from the kidney. These vessels—the renal artery and the renal vein—connect directly with the aorta and the vena cava, which are the major vessels that carry blood leaving and entering the heart.

The kidneys are highly complex organs whose main function is to remove waste products from the bloodstream and produce urine to excrete these

wastes. These organs also produce the hormone erythropoietin, which regulates the formation of red blood cells.

To help maintain the correct balance of water, salts, and acids in body fluids, the kidneys filter some of these substances out of the blood via approximately 2 million filtration units. Blood coming from the heart via the aorta enters the kidneys through the right and left renal arteries. Inside the kidneys, the renal arteries branch into smaller and smaller arterioles. Arteriole branching ends in microscopic glomeruli, which are masses of tiny, intertwined capillaries. Control of the chemical makeup of the blood and production of urine actually begin here. The thin walls of the glomeruli filter water, salts, sugar, and nitrogen-containing wastes (products of protein metabolism in the body) out of the blood. For the glomeruli to function well, blood-flow through the vessels of the kidneys must be maintained at a proper level. Should flow in the arterioles drop, the kidneys secrete renin, an enzyme that restores blood pressure by constricting the walls of these small vessels.

A cuplike structure surrounding each glomerulus collects the filtered substances and conveys them into the long, twisted renal tubule. Leading from the glomeruli to the renal pelvis, the tubule passes through another network of capillaries. Here, just the right amount of water, salts, and sugar are returned to the bloodstream. What remains is urine, containing excess water and a variety of waste products such as urea, creatinine, and uric acid. Every day a healthy adult produces about one to two quarts of urine, which leaves the renal pelvis via the ureter. This muscular tube extends out of the kidney at the hilum and transports urine to the bladder. Following temporary storage in the bladder, urine is excreted through another tube called the urethra.

Like other organs, the kidneys are composed of individual cells. Normally, growth and repair of tissues take place through the orderly division and reproduction of cells. When cell division is disordered, abnormal growth causes masses of tissue known as tumors to build up. These tumors may be benign or cancerous. Benign tumors may block normal organ function and may crowd adjacent organs, but they do not spread to other parts of the body and generally are not life threatening. Usually, benign tumors can be removed by surgery, and they are not likely to recur. Many scientists feel that certain small, benign

tumors in the kidney, called adenomas, are precursors to cancer; that is, they have the potential to become cancerous as they grow larger.

Cancers of the kidney can invade and destroy normal tissues and can extend into surrounding structures. Cancer cells also can break away from the primary tumor and metastasize, or spread, to other parts of the body through the lymphatic system or the bloodstream. When kidney cancers spread, the cells often migrate to the bones, lungs, liver, and brain, where they can continue to divide abnormally and form secondary tumors. Cancer cells that make up these secondary tumors are usually identical to those of the primary cancer, and although another organ of the body is affected, the disease is still kidney cancer.

Certain kinds of cancer have a tendency to spread to the kidneys. In fact, metastatic tumors in the kidneys are more common than cancers that actually begin there.

Several different types of cancer can arise in the kidney. Renal cell carcinoma of the cortex and transitional cell carcinoma of the renal pelvis almost always occur in adults. A different type of kidney cancer, called Wilms' tumor, develops only in children.

KIDNEY CANCER IN ADULTS

Renal cell carcinoma, the most common type of kidney cancer in adults, arises in the lining of the renal tubules. Also known as renal adenocarcinoma, hypernephroma, and Grawitz' tumor, it accounts for more than 85 percent of all adult kidney cancers. The next most common form is transitional cell carcinoma of the renal pelvis, which, in many ways, resembles bladder cancer. (Other cancers that originate in the kidney, mainly soft tissue sarcomas, are quite rare and are not discussed in this *Research Report.*)

Incidence

Cancer of the kidney accounts for about 2 to 3 percent of all cancers in American adults. Data collected and analyzed by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute show the following average incidence (the number of cases per year per 100,000 population) in the United States for cancers of the kidney and renal pelvis for the years 1978 to 1981: 10.0 for white males, 9.2 for black males, 4.4 for

white females, and 4.5 for black females. An estimated 20,000 cases of kidney cancer will be diagnosed in the United States in 1986.

Renal cell carcinoma affects twice as many men as women and is slightly more common among white men than black. It occurs most often between the ages of 50 and 70. Transitional cell carcinoma affects three times as many men as women, is twice as common among white males as black, and develops mainly after the age of 65.

Adult kidney cancers are more common in urban, industrialized areas, but there is little variation among different racial and ethnic groups. Worldwide, the incidence of renal cell carcinoma is higher in Northern Europe and North America and lower in Africa, Asia, and South America. For transitional cell carcinomas, rates are higher in the United States and Western Europe and lower in Japan and Scandinavian countries. Researchers have not found a satisfactory explanation for these geographic differences.

Cause and Prevention

The causes of kidney cancer are not fully understood, although scientists have identified some factors that increase risk for the disease. One such risk factor is tobacco use. Overall, smokers are twice as likely to develop kidney cancer as nonsmokers. Some researchers estimate that cigarette smoking is linked to 30 percent of kidney cancers in men and 24 percent in women. This link appears to be considerably stronger for transitional cell carcinoma than for renal cell carcinoma; in fact, recent studies implicate cigarette smoking as the major cause of cancer of the renal pelvis. For smokers, the risk of developing this type of cancer may be six to seven times higher than for nonsmokers, and the risk is apparently dose-related; that is, the more a person smokes, the higher the risk. One researcher calculates that more than 80 percent of renal pelvis cancers in men and more than 60 percent in women would be avoided if people stopped smoking.

Because they filter waste, the kidneys are exposed to many chemical substances, some produced by the body and others inhaled or ingested. A number of chemicals—such as nitrosamines, aflatoxins, lead acetate, and potassium bromate—do

cause renal cell carcinoma in laboratory animals. However, the same effect has not been observed in humans.

Scientists have known for some time that an increased risk of renal pelvis cancer is associated with heavy, long-term use of non-narcotic analgesic drugs. In recent studies, researchers isolated phenacetin as the particular analgesic that raised the risk of cancer of the renal pelvis. Furthermore, phenacetin and tobacco appear to act together in causing this disease. The risk for people who both smoke and use large amounts of phenacetin is 19 times that of the general public. It appears likely that phenacetin also may be implicated in some cases of renal cell carcinoma. (The Food and Drug Administration withdrew its approval for marketing phenacetin-containing products in 1983.)

As is true of several other forms of cancer, there is evidence that obesity may increase one's risk of developing cancer of the kidney. In several studies, obesity has been associated with increased risk in women, and one recent report suggests that being overweight may be a risk factor for men, too. The reasons for this are not clear. One hypothesis is that the increased risk in women may be related to an excess of the hormone estrogen produced in their fatty tissue.

The synthetic estrogen diethylstilbestrol (DES) can cause kidney cancers to develop in hamsters especially bred for use in research. However, researchers have not seen a greater-than-average risk of renal cell carcinoma in people treated with DES or other estrogens. One study did suggest a slightly increased risk of renal pelvis cancer in females using estrogen-containing drugs, but it was not proven that the drugs actually caused the disease.

In the laboratory, animals that have had one kidney surgically removed and are later exposed to ionizing radiation develop cancerous tumors in the second kidney. However, animals subjected to either the surgery or the radiation, but not both, do not have an unusual incidence of cancer in the remaining kidney. In humans, women treated with radiotherapy, mainly for certain disorders of the uterus, may have a slightly increased risk of developing cancer of the bladder and, possibly, the renal pelvis. Patients who were exposed to thorium dioxide, a radioactive substance used in the 1920's with certain diagnostic X-rays, have an increased rate of renal

cell carcinoma. However, this substance is no longer in use, and scientists think that ionizing radiation plays a minor role in the total number of kidney cancers.

A very small number of adult kidney cancers are familial. Certain inherited disorders (including von Hippel-Lindau's disease, tuberous sclerosis, Sturge-Weber syndrome, neurofibromatosis, and ataxia telangiectasia) put patients at increased risk for kidney tumors. A few familial cases not associated with one of these inherited conditions have been reported, but they are extremely rare.

Viruses cause kidney cancer in certain species of frogs, but there is no evidence that viruses contribute to the development of kidney cancer in humans. Kidney cancer is not transmissible from one person to another. Moreover, it is uncommon in people with immune disorders, who are susceptible to viral infections.

Recently, a number of studies have examined occupational exposures to see whether they raise workers' chances of developing kidney cancer. Some studies suggest that coke oven workers and insulation workers have above-average rates of kidney cancer, but suspect chemicals have not been identified. Among cadmium workers, a fourfold risk of renal cell carcinoma is seen in smokers, perhaps due to a synergistic effect similar to that seen for phenacetin and tobacco.

Researchers also have investigated several types of workplace exposure already linked with a higher incidence of bladder cancer. Reports now show that workers in the rubber, leather, petroleum, dye, textile, and plastics industries have an increased risk of transitional cell carcinoma of the renal pelvis. The rates of both types of kidney cancer in other occupations are under study.

Another concern is the recent observation that patients on long-term dialysis to treat chronic kidney failure have an increased risk of developing renal cysts and renal cancers. Further study is needed to determine how this finding may affect the care of patients with kidney failure.

Detection and Diagnosis

Detection

In its early stages, kidney cancer usually presents no obvious signs or troublesome symptoms. However, it is sometimes detected at an early stage during an examination for another condition or in the course of a routine checkup.

As a kidney tumor grows, it may cause symptoms that resemble those of other kidney diseases. The most common symptom is visible blood in the urine. Sometimes there is a lump or mass that can be felt in the kidney region and/or pain (a constant, dull ache) in the side, abdomen, or back. Other symptoms (known collectively as "paraneoplastic syndromes") occur less often but may lead the doctor to suspect cancer of the kidney. These include high blood pressure, intermittent fever, weight loss, fatigue, anemia, liver dysfunction, hypercalcemia (excess calcium in the blood), and erythrocytosis (an increase in red blood cells). These problems can be symptoms of cancer or a variety of other diseases.

Most cases of kidney cancer in adults (about 60 percent) are found only after the cancer has begun to spread. One goal of current research is to find ways of detecting the disease early. Researchers are working to identify a "biological marker," a measurable substance in the blood that could signal onset of the disease before symptoms appear, but at present, there are no reliable markers for kidney cancer. Some patients have elevated levels of renin, erythropoietin, or other chemicals in the bloodstream, but none of these is a consistent warning sign.

Researchers have developed a new animal model for both adult and childhood kidney cancers. A specially bred strain of mouse provides a much closer parallel to human kidney cancer than animal models used in the past. Scientists working with the mouse model have identified a number of hormones that are synthesized and secreted by adult kidney cancers and Wilms' tumor in humans. They hope that one or more of these hormones can form the basis for a simple blood test to screen individuals who are at above-average risk for kidney cancer.

Diagnosis

Renal cell carcinoma is often difficult to diagnose. Clues come from the physical examination, the patient's pattern of symptoms, and various laboratory tests. Improved imaging techniques now help to distinguish solid tumors (usually cancerous) from noncancerous, fluid-filled cysts. The diagnostic workup relies principally on X-ray examinations and may also include ultrasonography and blood and urine tests.

One of the first procedures used to diagnose a kidney problem is the excretory urogram, or intravenous pyelogram (IVP). This X-ray examination, performed with a contrast medium that usually contains iodine, provides a silhouette of the kidney, revealing any changes in the shape of the kidney, the ureter, or the neighboring lymph nodes.

If the IVP reveals a mass in the kidney, it is often followed by another series of X-ray studies called nephrotomography. This test, which gives a three-dimensional image of the kidney, can often distinguish a tumor from a cyst. In addition, computerized tomographic (CT) scans provide information about the size, density, extent, and other characteristics of the growth. CT scans also show involvement of the vena cava, renal vein, or regional lymph nodes.

Another test physicians sometimes use in the diagnostic process is ultrasonography. An ultrasound examination provides pictures from the echo patterns of soundwaves bounced back from internal organs. This technique may also help distinguish fluid-filled growths from solid ones.

Selective renal arteriography, which gives an X-ray image of renal blood vessels, is usually the final step in the diagnosis of kidney cancer. A substance opaque to X-rays is injected into the bloodstream, permitting doctors to see the veins and arteries that serve the kidneys. This test helps show the extent of a mass and is 95 to 98 percent accurate in diagnosing renal cell carcinoma. To confirm the diagnosis, doctors sometimes insert a needle into the tumor to withdraw sample cells for microscopic examination. This procedure is known as a fine-needle biopsy.

Doctors use additional tests to diagnose transitional cell carcinoma of the renal pelvis. The retrograde pyelogram is an X-ray picture taken after a contrast substance is injected into the kidney through the ureter.

With cystoscopy, a doctor can inspect the bladder through a lighted tube passed through the urethra. Urine and/or tissue can be analyzed for the presence of cancer cells. Also, researchers recently have developed a new device called a ureteropyeloscope, a lighted instrument that gives the doctor access to the ureter and renal pelvis without major surgery. It may even be possible to remove small tumors through the ureteropyeloscope, although the effectiveness of this technique remains to be tested.

A sensitive new diagnostic tool known as magnetic resonance imaging (MRI) can produce cross-sectional images of the kidney similar to those produced by computerized tomography. MRI, which employs only magnetic fields, does not expose the patient to ionizing radiation. Many researchers are enthusiastic about the potential of this new device, but its value in diagnosing kidney cancers must be defined by clinical studies.

Staging

Once kidney cancer has been found, other clinical and laboratory tests are used to establish the stage, or extent, of the disease. These tests usually include chest X-ray films, radioisotope bone and liver scans, abdominal CT scans, and blood tests. Additional X-ray studies of the renal blood vessels, the aorta, and the vena cava are sometimes needed to stage the disease and provide information the physician needs to plan the patient's treatment.

Stage I: The tumor appears to be confined to the kidney.

Stage II: The cancer involves the tissues that lie close to the kidney but has not spread beyond Gerota's fascia; cancer cells have not invaded regional lymph nodes or blood vessels.

Stage III: The cancer has invaded the renal vein, other blood vessels, and/or nearby lymph nodes.

Stage IV: The cancer has invaded neighboring organs or has spread to the opposite kidney or to distant sites in the body.

Treatment

Kidney cancer can often be cured if found and treated at an early stage, as it is in about 40 percent of all patients with the disease. Over the past three decades, progress has also been made against more advanced disease. Data from the NCI's SEER Program indicate that the overall 5-year relative survival rate for adult kidney cancer (combining patients of all races, both sexes, and all stages of disease) is 50 percent for those diagnosed between 1976 and 1981.

Improvements in survival appear to be due mainly to advances in surgical procedures, including better techniques in anesthesia and blood banking. Besides surgery, treatment may include radiation therapy, hormonal therapy, chemotherapy, and immunotherapy, depending on the stage and the specific needs of the patient. Integrated treatment, aggressive surgery in some cases for secondary tumors, intensive followup, and better supportive care have led to increases in the number of patients surviving 5, 10, and even 15 years. These are noteworthy achievements, particularly for a population in whom the average age at diagnosis is 55 to 60.

Surgery

Nephrectomy—the surgical removal of the kidney—was first used to treat adult kidney cancer in 1871. The remaining kidney generally is able to perform the work of both kidneys, and for more than a century this procedure has continued as the mainstay of treatment for adults with this disease. Experts generally agree that the more extensive "radical" nephrectomy, introduced in the 1950's, should replace "simple" nephrectomy as the standard surgical technique for most patients.

Simple nephrectomy is the surgical removal of just the kidney. In radical nephrectomy, the surgeon ties off the renal artery and vein and removes the kidney, as well as the adrenal gland (which lies just above the kidney) and some of the surrounding tissue. In addition, the surgeon usually removes the lymph nodes near the kidney, in case cancer cells have migrated there. Though some physicians question the therapeutic benefit of removing lymph nodes, they generally agree that this step can contribute to accurate staging.

Nephrectomy can cure most patients with localized kidney cancer (stage I); many in whom cancer cells have begun to spread from the kidney (stage II); and some with locally advanced tumors (stage III).

Nephrectomy is sometimes recommended for advanced or metastatic disease (stage IV) to control symptoms, such as excessive bleeding or abnormal hormone production, or to alleviate pain. For the 10 percent of stage IV patients who have a single metastatic tumor, further surgery to remove the secondary tumor has sometimes led to long-term survival.

Another technique—radical nephrectomy preceded by arterial embolization—is used to treat some patients diagnosed with large, locally advanced, or metastatic renal cancer. Small particles of a special substance such as gelatin sponge (Gelfoam) are injected into the renal artery through a very narrow tube called a catheter. This material blocks the small vessels that supply the tumor and thus deprives the cancer cells of nourishment. In some cases, preoperative arterial embolization may simplify later nephrectomy.

For certain patients—primarily those with small, less aggressive tumors and those with only one kidney—some physicians prefer to use a more conservative procedure, the partial nephrectomy. This method of treatment removes the tumor while preserving normal kidney tissue and, thus, kidney function.

Radiation Therapy

Clinical trials comparing the effectiveness of radiation before surgery with nephrectomy alone for stages I and II kidney cancer have not produced consistent results. Preliminary data from some recent research suggest that survival may be better among patients in the irradiated group. Other studies suggest that although survival time may not be improved, local recurrences may be decreased with preoperative radiation. Definitive answers will come from long-term followup of patients in studies like these.

Reports on the benefits of postoperative radiation have not produced clear-cut results yet, either. Some authorities think this mode of therapy may reduce local recurrence in patients with early stage disease and may also contribute to control of tumors that extend outside the kidney.

The importance of radiation therapy in alleviating problems caused by secondary tumors in the bone, lung, and abdominal wall is well established. It may also be useful in the care of certain patients with very large tumors or those who, for various reasons, cannot have surgery.

Hormonal Therapy

In clinical trials, hormonal treatment (usually synthetic forms of progesterone) has not been effective. However, doctors sometimes believe that trying this type of treatment is justified because some responses have been reported (especially in male patients with lung metastases).

Chemotherapy

At this time, anticancer drugs, successful in controlling many other forms of cancer, have not made important contributions in the treatment of kidney cancer in adults. Identifying effective drugs for patients with advanced disease remains a major challenge.

In early efforts to treat this disease with drugs, vinblastine (also known as Velban) appeared to hold promise, particularly if it could be given in high doses. However, more recent work has failed to demonstrate that vinblastine is effective in controlling cancer of the kidney in more than a small number of patients. Many other agents have been studied—both alone and in various combinations—with generally disappointing results. Nonetheless, researchers are continuing to look for new drugs, new drug combinations, and innovative ways of using existing ones.

Some of the new agents now under study for renal cell carcinoma include gallium nitrate, N-methylformamide, carboplatin, and 4'-deoxydoxorubicin. Antitumor drugs being evaluated for their effectiveness in treating transitional cell cancers of the urinary tract include methotrexate, dichloromethotrexate, and cisplatin.

Methotrexate, a drug used successfully for years in other cancers, is being given to patients with no evidence of metastasis following surgery for cancer of the renal pelvis in an attempt to determine whether chemotherapy can prevent or delay recurrences. In other clinical trials, investigators are trying to learn whether inoperable kidney tumors can be treated effectively by chemoinfusion, delivering anticancer drugs to the tumor directly through the renal blood supply, rather than through the general circulation. This approach might allow the use of larger and potentially more effective doses of the drugs, but it is a complex procedure that has not been studied adequately.

Some investigators believe that it may be possible to identify

useful antitumor drugs by growing human renal cancer cells in the laboratory and testing them for sensitivity to various agents. In addition, a new animal screening model may help accelerate studies of potentially useful therapies.

Immunotherapy

For the past several years, researchers have been actively exploring ways to enlist the body's immune system in fighting cancer. In both laboratory and clinical studies, scientists are evaluating a number of biological response modifiers (BRMs), natural and synthetic substances that may boost or strengthen the body's natural defenses against the disease. The results of recent studies with interferon, the best known of these agents, have been encouraging. Clinical trials suggest that interferon may be active against metastatic renal cell carcinoma, and further studies will test whether patients' responses can be improved by altering the doses and types of interferon.

In addition, in 1985, a team of NCI researchers reported the development of a new form of immunotherapy. Their approach uses a BRM called interleukin-2 (IL-2) to activate killer cells (a type of white blood cell) removed from the patient's blood. The result is a unique population of cells called lymphokine activated killer (LAK) cells. The patient is treated with the LAK cells and additional IL-2. In preliminary trials with a small number of patients, renal cell carcinoma appeared to respond to this type of immunotherapy. Clinical studies of this new approach are in progress at a number of institutions throughout the United States.

Physicians have observed long-term stabilization of secondary tumors in a few cases following embolization and nephrectomy. They theorize that interrupting the blood supply to renal tumors may cause the release of certain substances into the bloodstream and, through a series of complex steps, improve the body's natural antitumor response. However, this possibility has not been confirmed in controlled clinical trials.

WILMS' TUMOR

Incidence

The most common kidney cancer in children, nephroblastoma, has been called Wilms' tumor since 1899 when Dr. Max Wilms published his detailed paper describing the disease. About 500 new cases of Wilms' tumor occur in the United States each year. It accounts for 6 to 8 percent of childhood cancers. This disease affects 1 child in about 10,000 in this country, and the worldwide incidence is similar. Wilms' tumor occurs mainly in children under the age of 7, with most cases developing between the ages of 1 and 4. Boys and girls are affected equally.

Cause

The causes of Wilms' tumor are not known. The disease seems to be unrelated to race, climate, or environment, and it is apparently not linked to birth order, birth weight, maternal age, or maternal history of previous stillbirths.

About 10 percent of children with Wilms' tumor have certain congenital abnormalities. Aniridia (absence of the iris, the colored part of the eye) is seen in about 1 percent of children with Wilms' tumor, hemihypertrophy (abnormal, asymmetrical enlargement of one half or one part of the body) in about 3 percent, and various genitourinary defects in about 5 percent. Although the exact relationship of these conditions to kidney cancer is not understood, physicians who are aware of the occasional association can diagnose and treat Wilms' tumor at an early stage.

Scientists believe that there are both hereditary and nonhereditary forms of the disease. The hereditary type often arises at an earlier age and is likely to affect both kidneys or several sites in one kidney. Scientists suspect that a defective gene causes abnormalities in the fetal kidney, and chromosome studies point to a small region on the short arm of chromosome number 11 as the location of the defective gene(s). The proportion of Wilms' tumor patients whose families carry a genetic tendency toward the disease is not known. Moreover, researchers do not yet know whether the offspring of recovered Wilms' tumor patients are at higher risk of developing the disease.

Detection and Diagnosis

Detection

A swelling on one side of the upper abdomen is the most common symptom of Wilms' tumor. Other signs may include blood in the urine, low-grade fever, loss of appetite, paleness, weight loss, and lethargy. These problems are most often due to conditions other than cancer, but parents who observe such symptoms should consult a doctor promptly.

Diagnosis

The doctor takes a complete medical history and performs a physical examination. If Wilms' tumor is suspected, readily available diagnostic tests can lead to an accurate diagnosis in most patients. Blood tests to assess kidney and liver function are likely to be part of the initial workup. Production of excess erythropoietin may lead to erythrocytosis (an increase in the red blood cell count). Some patients may have abnormally high blood pressure believed to be caused by secretion of renin. Urinalysis is performed to detect blood in the urine.

The diagnosis of kidney cancer in a child depends primarily on imaging techniques (described on pages 9 and 10). The IVP is usually enough to identify Wilms' tumor. In some cases, ultrasonography and/or computerized tomography can help determine whether the abnormal growth is a solid tumor or a fluid-filled cyst. These tests can also show whether a cancerous growth has spread and can help determine if the opposite kidney is involved. Selective renal arteriography may be used if results of the other tests are inconclusive.

When clinical and laboratory data indicate kidney cancer, surgical exploration generally is the next step in diagnosing the disease. (Needle biopsies are seldom performed.)

Staging

Prognosis depends largely on the stage of the disease, or the extent of spread, at the time of diagnosis, and on certain microscopic features of the cancer cells. The staging system used most widely was developed by the nationwide association of cancer clinics and hospitals cooperating in the National Wilms' Tumor Study. This system takes into account the results of diagnostic tests, as

well as the observations of the surgeon and the pathologist.

Stage I: The tumor is confined to the kidney and is completely removed surgically. Nearly half of all children with Wilms' tumor have stage I disease.

Stage II: The tumor extends beyond the kidney but is still completely removed by surgery. Almost one-fourth of patients are in this group.

Stage III: The cancer is found in surrounding tissues, lymph nodes, or blood vessels in the abdomen and cannot be entirely removed by surgery. Nearly one-fifth of children with Wilms' tumor are in stage III.

Stage IV: Cancer cells have spread and formed secondary tumors at distant sites, most commonly the lungs, liver, bone, and brain. About 5 percent of Wilms' tumor cases are described as stage IV.

Stage V: Cancer is bilateral, affecting both kidneys, at the time of diagnosis. The disease is in stage V in about 5 percent of Wilms' tumor cases.

Each tumor is designated "favorable histology" (FH) or "unfavorable histology" (UH), as determined by the pathologist. While all cancer cells lack the orderly arrangement of normal cells, those designated UH are especially primitive and extremely lacking in organized microscopic structure. The vast majority of children diagnosed with kidney cancer (about 90 percent) have cell types described as favorable. (Kidney tumors that contain elements of sarcoma—cancer that arises from supportive or connective tissue rather than from lining tissue—are also designated UH, although most specialists believe that these cancers are a different disease and should not be classified as Wilms' tumor.)

Treatment

In general, children respond better than adults to cancer therapy, and this advantage is especially clear in the treatment of kidney cancer. Wilms' tumor is one of modern medicine's

success stories. Treatment plans that combine modern techniques in surgery, radiotherapy, and chemotherapy have brought dramatic progress in treating this disease. How the various treatment methods are combined depends on the extent and cellular characteristics of the cancer, as well as the child's medical history, general health, and age.

Experience has shown that children treated for Wilms' tumor can be considered cured if they survive for 2 years without any sign that the disease has returned. In the early part of this century, Wilms' tumor was almost invariably fatal; only a few children survived as long as 2 years after diagnosis. Statistics now show that nearly 80 percent of children with Wilms' tumor are being cured; in those with favorable histological types, the cure rate approaches 90 percent. The small number of children with aggressive cell types (unfavorable histology) or with widespread disease at the time of diagnosis have a poorer outlook, but many of these patients are curable with intensive therapy.

Surgery

In the 1930's and 1940's, improvements in surgery, anesthesia, and pre- and postoperative care made it possible to perform nephrectomies successfully in very young patients. As a result, about 40 percent of children with Wilms' tumor survived the disease. Radical nephrectomy (described on pages 11 and 12) remains the cornerstone of treatment for Wilms' tumor.

Radiation Therapy

Although the value of radiotherapy for adult kidney cancer is still questionable, it can be important in the treatment for Wilms' tumor. Since 1915, doctors have recognized that Wilms' tumor responds to radiation therapy. By the 1950's, the combination of nephrectomy and postoperative radiation therapy had yielded survival rates of almost 50 percent.

Chemotherapy

The next major advance was the discovery that certain drugs, particularly actinomycin D and vincristine, could reduce the size of Wilms' tumors. These drugs were tested for safety and effec-

tiveness in a series of small-scale clinical studies starting in the 1960's. In one study, investigators found that a 15-month course of repeated treatment with actinomycin D was superior to a single dose of the drug given after surgery. Since then, "maintenance" therapy of varying lengths has been an accepted principle of drug treatment for Wilms' tumor.

After the addition of chemotherapy, treatment centers began adopting a modern team approach in caring for Wilms' patients. With pediatric surgeons, radiotherapists, and oncologists working together, these centers have consistently reported overall 2-year survival rates of 70 to 80 percent.

Side Effects

Although each form of cancer treatment can be accompanied by undesirable effects, all patients do not have the same problems, nor do they experience difficulties to the same degree. Chemotherapy and radiotherapy often cause nausea and vomiting, but these problems are temporary and usually can be curbed with medication. A more serious short-term side effect is the suppression of bone marrow. In killing cancer cells, chemotherapy and radiotherapy also destroy some normal cells in the bone marrow. If the white cells, red cells, and platelets fall too low, patients can become susceptible to bleeding and infection. Such reactions are temporary, and supportive care, such as antibiotic therapy, helps to protect patients from these complications during their treatment.

Pediatric oncologists are particularly concerned with adverse effects that may appear long after successful cancer treatment. For example, radiation therapy can disrupt normal bone growth, especially in very young children. Irradiation can also injure organs, disturb hormonal and reproductive functions, and, in a small percentage of cases, induce new cancers years after therapy. Doctors are also concerned that chemotherapy may cause new primary cancers to develop many years later.

Beginning in the 1960's, as more and more children were being cured of Wilms' tumor, researchers began to examine the accepted treatment programs in an effort to reduce the complications of therapy. Since that time, a series of clinical trials has been designed to identify treatment methods to give Wilms' patients the best chance

of being cured while sparing them as many complications as possible. Investigators continue to explore more aggressive approaches to improve the outlook for patients whose tumors are resistant to standard treatment.

National Wilms' Tumor Study

Because Wilms' tumor affects only a small number of children, researchers recognized that pooling resources and data would help speed answers to important questions about improvements in treatment. In 1969, the National Wilms' Tumor Study (NWTS), a national consortium of hospitals and clinics treating children with cancer, was created with National Cancer Institute support to carry out controlled clinical trials. Since then, treatment for Wilms' tumor has been refined in a series of studies enrolling more than 2,300 patients. In the first study (NWTS-1), carried out between 1969 and 1974, the overall 2-year survival rate was 80 percent. The second trial (NWTS-2), which ended in 1978, achieved a 2-year survival rate of 87 percent. The treatment currently received by most Wilms' tumor patients in this country is based on the results of these studies. (NWTS-3 is still in progress.)

NWTS-1 found that stage I patients under 2 years of age given actinomycin D did not require postoperative radiotherapy. The first trial also showed that, for stages II and III, the combination of actinomycin D and vincristine was superior to either drug used alone.

Data gathered in NWTS-2 revealed that combination chemotherapy could replace radiotherapy in the treatment of stage I patients, regardless of the child's age. (At present, postoperative irradiation is generally reserved for patients with unfavorable histology or more advanced disease.)

NWTS-2 also demonstrated that the period of maintenance chemotherapy could be cut from 15 months down to 6 months without changing the cure rate for stage I patients. In addition, the second study showed that treatment of more advanced cases could be improved by adding a third drug, Adriamycin, to the other two. (The three-drug combination also is used for less advanced cases with unfavorable histology.)

When the third study began in 1979, analysis of the NWTS experience showed an overall 2-year survival rate of 89 percent for cases with favorable

histology, but only 39 percent for those with unfavorable histology. With this strong evidence of the impact of histologic tumor characteristics on prognosis, NWTS-3 was designed to evaluate the effectiveness of therapy that is more limited for patients in the FH group and more aggressive for those in the UH group.

Preliminary results of this ongoing study, reported in May 1984, suggest that tumors designated FH can be successfully treated with less intensive regimens. For example, NWTS-3 investigators have found that for stage II-FH, results after intensification of the standard two-drug combination (by the addition of either Adriamycin or radiation therapy) apparently are not improved. Also, evidence to date indicates that stage III-FH patients treated wtih three-drug combination chemotherapy and low doses of radiation have done just as well as a similar group treated with more intense radiotherapy.

NWTS-3 has also evaluated the benefits of adding cyclophosphamide to the three drugs in current use for patients with advanced disease (stage IV) and those with unfavorable histology at any stage. The four-drug combination does not appear to offer these children a significant advantage, and researchers now are considering other ways of improving the care of patients with metastatic disease or unfavorable cell types.

PDQ

The National Cancer Institute has developed PDQ (Physician Data Query), a computerized database designed to give doctors quick and easy access to:

- the latest treatment information for most types of cancer;
- descriptions of clinical trials that are open for patient entry; and
- names of organizations and physicians involved in cancer care.

To get access to PDQ, a doctor may use an office computer with a telephone hookup and a PDQ access code or the services of a medical library with online searching capability. Most Cancer Information Service offices (1-800-4-CANCER) provide a physician with one free PDQ search and can tell doctors how to get regular access to the database. Patients may ask their doctor to use PDQ or may call 1-800-4-CANCER themselves. Information specialists at this toll-free number use a variety of sources, including PDQ, to answer questions about cancer prevention, diagnosis, and treatment.

Suggestions for Additional Reading

Except as noted, the following materials are not available from the National Cancer Institute. They can be found in medical libraries, many college and university libraries, and some public libraries. Information about ordering NCI materials is provided at the end of this publication.

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Young People With Cancer: A Handbook for Parents, prepared by the Office of Cancer Communications, National Cancer Institute. NIH Publication No. 83-2378.

Additional Information

For additional information on this subject and for other NCI publications, write to the Office of Cancer Communications, National Cancer Institute, Bethesda, Maryland 20892, or call the Cancer Information Service (CIS) toll-free at

1-800-4-CANCER*

*In Alaska, call 1-800-638-6070; in Hawaii, on Oahu call 524-1234 (call collect from neighbor islands).
Spanish-speaking CIS staff members are available to callers from the following areas (daytime hours only): California, Florida, Georgia, Illinois, northern New Jersey, New York, and Texas.

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